REMARKS

Claims 1, 3, and 35-58 are pending in the instant Application.

Amendments to the Claims

Claims 1, 3, and 35-58 are pending in the instant Application. With the instant amendments, Applicants amend claims 1, 3, 35, 47, 49, and 55, and introduce new claims 59-61. All such amendments and new claims are supported by the specification as filed.

The amendments to claim 1 are of a ministerial nature and merely replace the providing and outputting steps by references to, respectively, the amino acid sequence and predicted structure, in other steps.

Claims 3 and 35 are amended to correspond to text in the specification as filed, at page 7, end of paragraph [0015].

Claim 47 is amended to recite limitations found in the specification as filed at page 14, paragraph [0031].

Claim 49 is amended to correct a lack of antecedent basis for the term 'membrane.'

Claim 55 is amended to recite the fact that the second molecular dynamics simulation is performed for a time in the range from about 100 ps to about 1 ns. This amendment is supported by the specification as filed at page 18, at the end of paragraph [0034].

New claim 59 is supported by the specification as filed at page 15, paragraph [0032].

New claim 60 is supported by the specification as filed at page 11, paragraph [0026].

New claim 61 is supported by the specification as filed at page 18, paragraph [0035].

New claim 62 is supported by the specification as filed at pages 21-22, paragraph [0042].

Accordingly, no new matter is presented by way of the claim amendments and new claims, and entry thereof is respectfully requested.

REJECTIONS OF THE CLAIMS

Applicants have reviewed the final Office Action mailed September 29, 2005 (the "Final Office Action") and considered the grounds of rejection presented therein. Applicants note that, from a reading of the Final Office Action, no specific grounds of rejection has been articulated for claim 43. Accordingly, Applicants presume that this claim at least, is in condition for allowance, and an indication of the same is respectfully requested.

As a preliminary matter, Applicants note that no new grounds of rejection are presented in the Final Office Action. In fact, the rejections of various claims in the Final Office Action are on the same statutory grounds as those stated in the Office Action mailed January 14, 2005 (the "January 14, 2005 Office Action"). However, the rejections of the various dependent claims in the Final Office Action are presented in an abbreviated form, without identifying the pertinent teachings in the cited references that the Office deems applicable to such claims. Pertinent teachings were, however, set forth in the January 14, 2005 Office Action. Therefore, Applicants' remarks herein rebut both the abbreviated rejection as presented in the Final Office Action, as well as the statements of rejection presented in the January 14, 2005 Office Action.

Rejections under 35 U.S.C. § 102

Claims 1, 36-38, 41-42, 44-46, 48, and 51-58 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by a review article by Biggin and Sansom ("Interactions of α-helices with lipid bilayers: a review of simulation studies", *Biophysical Chemistry*, 76:161-183 (1999)), hereinafter "Biggin." Applicants respectfully traverse the rejection because Biggin does not disclose each and every element of the recited claims, and also because the rejection as stated has not pointed out where each claim element is to be found in the cited reference.

Applicants first remind the Examiner of the applicable law in this area. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thus, similarity between a cited reference and a claimed invention is not sufficient to sustain a finding of anticipation. Additionally, the elements must be arranged in the reference as required by the claim (though this is not an *ipsissimis verbis* test, *i.e.*, identity of terminology is not required), *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). See also *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 48 USPQ2d 1225 (Fed. Cir. 1998) ("[w]hen the defense of lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims, arranged as in the patented device."). Applicants respectfully point out that Biggin neither

teaches each and every element of Applicants' claims, nor describes Applicants' invention in complete detail.

Given the somewhat protracted nature of prosecution in the instant application, Applicants take this opportunity to illuminate the record with a clear statement of how the instant invention is distinguishable from the cited references.

As set forth in Applicants' specification, Applicants' "invention provides a hierarchical protocol using multiscale molecular dynamics and molecular modeling methods to predict the structure of G-protein Coupled Receptors" (Specification at page 6, ¶ [0014]). In particular, it is the application in sequence of several steps, including identification of transmembrane portions of a peptide sequence, construction of helices and inter-helical loops, and two separately applied molecular dynamics steps, that distinguishes the claimed invention over Biggin.

In essence, as is further discussed hereinbelow, the Office's rejection is based upon an insufficient showing that various claim elements are to be found in Biggin. The Office's findings are not sufficient to meet the legal requirements of anticipation. Thus, according to the Examiner:

> Biggin discloses modeling and simulation studies of membrane proteins comprising steps of
>
> providing an amino acid sequence for a membrane-bound protein,
> identifying a range or ranges of amino acids as transmembrane regions
> constructing helices
> optimizing a helix bundle configuration
> constructing inter-helical loops to generate a full-atom model
> optimizing the full-atom model, and
> outputting a predicted structure
>
> as set forth in the previous office action mailed 1/14/2005.

Final Office Action at page 2 (formatting added herein). Applicants respectfully submit that the Office's conclusion that anticipation can be shown is not borne out by a study of Biggin because Biggin does not teach all of the recited steps.

Before progressing, it is instructive to consider the teachings of Biggin in their totality. Biggin reviews simulation studies of systems having one or more α-helices that interact with a lipid bilayer. In particular, Biggin references examples of molecular dynamics methods that have been employed to carry out such simulations (Biggin, section 1, page 161). Biggin describes, phenomenologically, two distinct orientations of an α-helix in a lipid bilayer, 'surface'

and 'inserted' (Biggin, section 2, pages 161-162 and in particular Fig. 1). These are features of the bilayer system to be modeled, not facets of a modeling method. Biggin goes on to describe separately features of the first of these orientations, an α-helix at the surface of a bilayer (Biggin, section 3, pages 163-164) and the second, an α-helix spanning the bilayer (Biggin, section 4, pages 164-165), as well as the transition between the two orientations (Biggin, section 5, pages 165-166). Thus, the first five sections of Biggin describes the types of systems to which molecular dynamics simulations have been applied without describing in any detail such methods of simulation.

Biggin then describes two different categories of simulations: 'mean-field' simulations (Section 6, pages 166-170) and 'all-atom' simulations (Section 7, pages 170-180). As stated by Biggin, the two different categories of simulations have been applied in different ways. In particular, in mean-field simulations, "the solvent and bilayer environments [are treated] as a continuum" (Biggin, section 6.1 at page 166), whereas in all-atom simulations, "both the lipid molecules and the water ... are represented atomistically" (Biggin, section 7.1 at page 170). Thus, Biggin describes, simply, the fact that two types of simulations have been applied to membrane-bound proteins, and that the different types of simulations offer different qualitative results and advantages. The concluding paragraph of Biggin (Section 8, page 180) offers a prospect to "exploit the results of atomistic [*i.e.*, all-atom] simulations to improve the quality of mean field simulations." Thus, Biggin suggests that a desirable goal is an improvement to mean field simulations, but without suggesting precisely how this is to be accomplished.

The rejection as cast in the January 14, 2005 Office Action

Considering claim 1 now, step by step, it is necessary to refer to the January 14, 2005 Office Action, which offers the following bases for the rejection.

> Regarding the preamble and first steps of claim 1, the Office states:
>
> 19. Biggin et al. discloses computer method simulations predicting membrane bound proteins comprising a plurality of α-helix [*sic*] (Abstract et al.), as in instant claim 1, lines 1-3.
> 20. Biggin et al. provides amino acid sequences for said membrane-bound proteins wherein bacteriorhodopsin has as [*sic*] set [of] 7 helices comprising transmembrane regions. It is noted that in Table 1 '[o]nly the sequence of the TM helix is given, even though simulations included the entire sequence (page 169, Table 1) as in instant claim 1, lines 4-7, and claim 37.

(January 14, 2005 Office Action, at page 5). Applicants respectfully point out that, at least the disclosures of Biggin referenced in item no. 20 of the January 14, 2005 Office Action do not teach the steps of the instant claim to which the Office has applied them.

In particular, the relevant portion of instant claim 1, as amended herein, recites "identifying a range of amino acids in an amino acid sequence for the membrane-bound protein as transmembrane regions of the membrane-bound protein". Biggin provides no such teaching of "identifying a range of amino acids ... as transmembrane regions." Table 1 of Biggin, referenced by the Office is irrelevant to this portion of the claimed method because it merely lists sequences of helices. It does not show how such sequences were identified, either as helices, or whether they themselves are transmembrane regions, as required by the claim. (The footnote referenced by the Office, purporting to show that the helices in Table 1 are transmembrane portions of an entire sequence, demonstrates nothing about how one might identify a transmembrane sequence region, and also applies only to protein Pf1.) In fact, identification of transmembrane regions can be carried out as described in Applicants' specification at paragraph [0028], pages 12-13. No such method is disclosed or described in Biggin.

The next step of claim 1 recites "constructing each of two or more helices in a set of helices for the transmembrane regions". However, the Office does not demonstrate if, or where, such a step can be found in the teachings of Biggin. The "constructing" step comprises using at least "secondary structure modeling techniques" (specification at paragraph [0029], page 13). No such techniques are disclosed in Biggin.

Regarding a further step of claim 1, the Office states:

> 21. Biggin et al. discloses using mean-field membrane simulations (first simulation) to provide a useful means to obtain information about possible conformations and/or orientations of a protein (pages 166-170, §§6.1 to 6.2), as in instant claim 1, lines 8-9.

(January 14, 2005 Office Action, at page 5). While it is true that Biggin discloses mean-field simulations of a transmembrane protein, as further discussed herein the disclosure of Biggin fails to recite other steps of the claimed method.

The next step of claim 1 recites "after optimizing the helix bundle configuration, constructing one or more inter-helical loops to generate a full-atom model of the membrane-bound protein". However, the Office does not demonstrate if, or where, such a step can be found

in the teachings of Biggin. This step comprises using, typically, "loop-building software" (specification at paragraph [0032], page 15). No such technique is disclosed in Biggin.

In respect of the penultimate step of claim 1, the Office states:

> 22. Biggin et al. discloses, in the all atom simulations (page 170, §7), TM helix bundle models may be constructed by less costly simulations without bilayer, then refined (optimize) by subsequent (second simulation, etc.) MD simulations in an atomistic bilayer or bilayer-mimetic environment. *** Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines), as in instant claim 1, lines 10-12.

(January 14, 2005 Office Action, at page 5). While it is true that Biggin discloses all-atom simulations, as further discussed herein this disclosure by itself is not sufficient to support a finding of anticipation of claim 1 or the claims depending therefrom because other steps of claim 1 are not to be found in Biggin.

Finally, for the last step of claim 1, the Office states:

> 23. The predicted structure has been outputted based on the all atom simulations (page 178, Figure 9), as in instant claim 1, lines 13-14.

(January 14, 2005 Office Action, at page 5). While it is true that Biggin discloses outputting a structure, once again, this disclosure by itself is not sufficient to support a finding of anticipation of the claims because, as previously stated, other steps of the claimed invention are not to be found in Biggin.

In summary, Biggin does not anticipate claim 1 at least because it does not recite several steps of the claim. In particular, Biggin does not teach identifying a range of amino acids in an amino acid sequence for the membrane-bound protein as transmembrane regions of the membrane-bound protein, and Biggin does not teach constructing helices, and does not teach constructing one or more inter-helical loops therebetween. The Office has not satisfied the requirements of showing an anticipation for at least these reasons. At best, the Office has argued mere similarity between Biggin and the claimed methods, which as referenced above, is insufficient grounds to find anticipation.

The rejection as cast in the Final Office Action

Now, with respect to the Office's additional justifications, in the Final Office Action, that Biggin anticipates the claims of the instant invention, Applicants respectfully offer the following rebuttals.

The Office states that:

> Biggin's method simulates a membrane-bound protein structure in various environments ... (*see*, for example, p. 162, left col. and p. 171). The instant method also simulates a membrane-bound protein structure in an environment ... (*see* instant claim 46 and the specification p. 14, lines 6-9, and fig. 4, step 460).

Final Office Action, at page 3. Notwithstanding the accuracy of the Office's characterization of the various teachings, mere similarity between the goals (simulation of a membrane-bound protein) of a claimed method and the teachings of a reference is insufficient to find anticipation. Even to the extent that such a similarity is germane to instant claim 46, the remaining steps of claim 46 (*i.e.*, those of claim 1, from which it depends) must be identified in the cited reference. As discussed hereinabove, the Office has not identified such steps.

The Office then states that "Biggin teaches 'modeling and simulation studies of membrane proteins and of their interactions with lipid bilayer' ... (p. 162, left col.)" (Final Office Action, at page 3). Again, notwithstanding the accuracy of this statement, it cannot support a finding of anticipation of any of the instant claims without a showing that the cited reference recites each and every element of the claimed methods. See, *e.g.*, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226.

The Office states further that "Biggin discloses a two-stage model of membrane protein folding (p.162, right col.)." (Final Office Action, at page 3). Applicants disagree that the disclosure in question is relevant to Applicants' claimed invention. Specifically, the "two-stage model" at page 162 of Biggin refers to a proposed model of protein folding having a first stage in which "independently stable units of secondary structure are formed first," and a second stage in which "[t]hese [units] self-assemble to form tertiary structure." As such, it is not a disclosure of a two-stage method of modeling such a protein in which each stage is modeled by separate simulations, as recited in Applicants' claims. On the contrary, it is a reference to a suggested model in which a protein molecule assembles *in vivo*; *i.e.*, it is a proposed explanation of how an actual protein molecule folds in nature.

Next, the Office references the fact that "Biggin states that 'simulation studies of TM [transmembrane] helices and TM helix bundles will help us to understand the principles of the structure' (page 165, left col.)" (Final Office Action, at page 3). However, the relevance of this

statement is unclear since a mere allusion to a desirable goal is insufficient, by itself, to support a finding of anticipation.

Further, the Office states that "Biggin discloses that several algorithms exist for predicting the number and position of model TM helices within a membrane protein sequence (p. 174). Further, Biggins [*sic*] states that MD simulations of model TM helices may be used to refine the results of such prediction (page 174)" (Final Office Action, at page 3). Again, a mere disclosure that a number of algorithms exist is not an indication that any one of them has either been described, or anticipates the claimed invention. Furthermore, the statement that MD simulations may be used to refine results of the prediction obtained with another method is not, in itself, a disclosure that anticipates the claimed invention.

Finally, the Office states that

> Biggin illustrates the refinement on M2 protein from influenza wherein TM helices were simulated (p.174). Bigggin discloses a helix bundle simulation in a POPC bilayer (fig. 9). Thus, Biggins [*sic*] does provide for a method of simulation similar to the instant method.

(Final office Action, at page 3). Notwithstanding the fact that Biggin does describe examples of simulation studies on various proteins, neither this nor the other disclosures referenced by the Office is sufficient to sustain the Office's conclusion that Biggin provides a "method of simulation *similar* to the instant method". (Final Office Action at page 3, emphasis added herein.) Even if such similarity had been shown, which as discussed above it has not, mere similarity between a reference and a claimed method is not sufficient to support a finding of anticipation. See, *e.g.*, *Jamesbury Copr. V. Litton Industrial Products, Inc.*, 756 F.2d 1556, 225 USPQ 253 (Fed. Cir. 1985) (instruction that a patent was invalid of lack of novelty if the prior art 'disclosed substantially the same things' was erroneous). See also *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 227 USPQ 3337 (Fed. Cir. 1985) *remanded* 475 U.S. 809, 229 USPQ 478 (1986), *on remand* 810 F.2d 1561 (1, USPQ2d 1593, (Fed. Cir. 1987), *cert denied* 481 U.S. 1052 (1987 ("concepts do not anticipate").

In conclusion, Biggin does not anticipate claim 1 and, accordingly, Applicants respectfully request that the rejection of record be removed.

Rejections of claims 36-38, 41, 42, 44-46, 48, and 51-58

Notwithstanding the fact that, if Biggin does not anticipate claim 1, then it cannot also anticipate any claim that depends – directly or indirectly – from claim 1, in the interests of expediting prosecution Applicants address the individual grounds of rejection of certain claims where it is desirable to point out that a further specific teaching is not to be found in Biggin.

Referring to the January 14, 2005 Office Action for a statement of rejection of each dependent claim, Applicants respectfully traverse as follows.

Regarding Claim 38, reciting "determining a periodicity of hydrophobic residues," the Office references Biggin (p. 166, col. 2) for "use of a hydrophobicity index to represent the presence of a *lipid* bilayer" (see Item 25 on page 6 of January 14, 2005 Office Action, emphasis added). However, the claim recites the periodicity of hydrophobic *residues*, *i.e.*, parts of the protein. Biggin recites using a hydrophobicity index to represent the lipid bilayer, not a protein. Thus, Biggin does not teach the elements recited in claim 38.

Similar considerations apply with respect to claim 44, which recites "identified lipid-accessible residues". Such residues are part of the protein and not the lipid bilayer.

Regarding claim 41, which recites "constructing each of two or more helices ...", it is unclear why the Office references page 178 of Biggin (see Item 26 on page 6 of January 14, 2005 Office Action). The rejection of claim 41 as anticipated by Biggin should either be withdrawn, or further clarification should be provided.

In respect of claim 45, reciting a "rigid body molecular dynamics simulation", the Office cites simulations that allegedly yield "stable (rigid) helix bundles", as found on page 179 of Biggin, at column 1 (see Item 28 on page 6 of January 14, 2005 Office Action). The Office is wrong to equate the term 'stable' as used by Biggin, with 'rigid body' as recited in the instant claim. As shown in Applicants' specification (page 14, paragraph [0031]), rigid body dynamics refers to simulations carried out with a particular type of force field. The term 'stable' as used in the referenced portion of Biggin refers to whether a particular configuration of a helix bundle deviates significantly during a simulation. Stability of a helix configuration is an attribute independent of the form that is chosen to model it.

Finally, it is noted that no specific grounds of rejecting claim 37 under 35 U.S.C. § 102(b) has been articulated by the Office. In the absence of a showing that the recited elements of claim 37 are found in the art, Applicants respectfully request that the rejection be removed.

In summary, Biggin does not anticipate any claim that depends from claim 1 for reasons presented above. Accordingly, the rejection of claims 36-38, 41, 42, 44-46, 48, and 51-58 over Biggin should be removed.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 3, 35, 39, 40, 47, 49, and 50, under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of one or more other cited references.

The U.S. Patent and Trademark Office ("PTO") bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, the PTO must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings in the manner suggested by the PTO. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Second, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would be successful. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Rejection over Biggin in view of Rose

The Examiner has rejected claims 3, 35, 39, 40, 47, 49, and 50 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of U.S. Patent No. 5,680,319 to Rose *et al.* ("Rose"). Applicants respectfully traverse the rejection, at least because the cited references do not, either alone or in combination, teach every element of the claims.

In the first instance, as has been established hereinabove, Biggin does not teach each and every element of claim 1. Furthermore, as acknowledged by the Examiner, Biggin does not teach additional elements of claims 3 and 35. The deficiencies of Biggin are not provided by Rose.

Claim 3 recites "constructing each of two or more canonical helices corresponding to the transmembrane regions". The Examiner has identified an untitled conformation table at cols. 5-6 of Rose as purportedly disclosing canonical helices (January 14, 2005 Office Action, at page 8, paragraph 41). However, the Examiner has not identified what attributes, if any, of these helices merit the description 'canonical'. Since claim 35 depends from claim 3, similar considerations apply to the rejection of claim 35.

However, even if it can be shown that a combination of Biggin and Rose recites each and every element of claims 3 and 35, the Examiner's offered motivation to combine their respective teachings is improper for at least the following reasons. Biggin, as previously discussed, reviews two types of molecular dynamics simulation for membrane-bound proteins, the mean-field approach, and the all-atom approach. Biggin does state, as referenced by the Examiner, that it would be desirable to exploit results of all-atom calculations to improve mean-field calculations. However, this is no more than a desire, without any guidance of how it could be accomplished. The Examiner has not articulated why such a desire leads to Applicants' claimed invention. The teachings of neither Biggin nor Rose give any indication of how such an improvement, were it to be relevant, would be implemented. Rose is totally silent with respect to any mention of the mean field approach which, as Biggin states, is employed for simulating the effects of membrane and solution environments. In fact, Rose makes no mention of either lipids or bilayers in its entire specification and claims. On the contrary, Rose is directed to methods of predicting protein folding mechanisms. As such, Rose addresses a different problem in the art (how a protein adopts a three-dimensional configuration, starting from a sequence of amino acid residues) from the problem addressed by Biggin (simulation of dynamical behavior of three-dimensional protein structure in a membrane). Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of Biggin and Rose.

Rejection over Biggin in view of Mathiowetz

The Examiner has rejected claims 39, 40, 49 and 50 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of Mathiowetz, *et al.*, *Proteins: Structure, Function, and Genetics*, 20:227-247 (1994), ("Mathiowetz"). Applicants respectfully traverse the rejection, at least because the cited references do not, either alone or in combination, teach every element of the claims.

In the first instance, as has been established hereinabove, Biggin does not teach each and every element of claim 1. Furthermore, as acknowledged by the Examiner, Biggin does not teach additional elements of claims 39, 40, 49 and 50, which all depend directly or indirectly from claim 1. Even if it is accepted that Mathiowetz provides deficiencies of these claims, the rejected claims are not obvious over a combination of Biggin and Mathiowetz at least because of the deficiencies of Biggin.

Additionally, even if it could be shown that a combination of Biggin and Mathiowetz disclosed the elements of claims 39, 40, 49 and 50, one of ordinary skill in the art would not have been motivated to combine the teachings of Biggin and Mathiowetz for the following reasons.

In respect of claims 39, 40, 49, and 50, the Examiner's stated motivation to combine the respective teachings of Biggin and Mathiowetz is improper for at least the following reasons. Biggin reviews the mean-field and the all-atom approaches to molecular dynamics simulation of membrane-bound proteins. Biggin does suggest, as referenced by the Examiner, that it would be desirable to exploit results of all-atom calculations to improve mean-field calculations. However, as mentioned in regard to the rejection of claims 3 and 35, this is no more than a desire. The teachings of neither Biggin nor Mathiowetz give any indication of how such an improvement would be implemented. Significantly, Mathiowetz is makes no mention of the mean field approach. Furthermore, Mathiowetz is directed to methods of calculating non-bonded interactions in molecular dynamics simulations of proteins. As such, Mathiowetz addresses a different problem in the art from the problem addressed by Biggin. Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of Biggin and Mathiowetz.

Regarding claim 49, the Examiner references Biggin's disclosure of "stable (rigid) helix bundles". Applicants respectfully draw the Examiner's attention to remarks presented hereinabove, regarding the rejection of claim 45. In short, rigid body molecular dynamics simulation is not the same as considerations of stability of a helix bundle configuration. A

Rejection over Biggin in view of Mayo

The Examiner has rejected claim 47 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of Mayo, *et al.*, *J. Phys. Chem.*, 94:8897-8909 (1990) ("Mayo"). Applicants

respectfully traverse the rejection, at least because there is no motivation to combine the cited references.

In the first instance, as has been established hereinabove, Biggin does not teach each and every element of claim 1. Furthermore, as acknowledged by the Examiner, Biggin does not teach additional elements of claim 47. Accordingly, for at least this reason and notwithstanding the teachings of Mayo, the rejected claims are not obvious over a combination of Biggin and Mayo.

Nevertheless, the Examiner's stated motivation to combine the respective teachings of Biggin and Mayo is improper for at least the following reasons. Biggin reviews approaches to molecular dynamics simulation of membrane-bound proteins. Biggin does suggest, as referenced by the Examiner, that it would be desirable to exploit results of all-atom calculations to improve mean-field calculations of such proteins. However, as mentioned in regard to the rejection of claims 3, 35, 39, 40, 49 and 50, this is no more than a desire. The teachings of neither Biggin nor Mayo give any indication of how such an improvement would be implemented. Significantly, Mayo makes no mention of the mean field approach. Furthermore, Mayo is directed to a new generic force field for molecular simulations, DREIDING. In particular, DREIDING is described as having generic application to all molecules that would be considered in drug design applications, as distinct from other force fields (such as AMBER, CHARMM, MM3, OPLS) that have been tailored to fitting properties for selected types of molecules, such as proteins and nucleic acids (Mayo, Introduction at page 8897). Furthermore, one of ordinary skill in the art, reading Mayo, would see that the principal examples of application of DREIDING are small organic molecules (see Mayo, pages 8901-8903) and thus would not immediately think that DREIDING has been specifically tailored for use in mean field simulations of proteins. Finally, Mayo acknowledges that the "calculations reported ... are all for molecules in vacuum or for molecular crystals". This would suggest to one of ordinary skill in the art that DREIDING would not be the first force field of choice to be combined with the teachings of Biggin for the purposes of improving the mean field approach, because the mean field approach is applied to simulating effects of solvent and lipid environment. Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of Biggin and Mayo. The Examiner is reminded that the teaching or suggestion to make the

claimed invention must be found in the prior art, not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

In summary, claims 3, 39, 40, 47, 49, and 50 are not obvious over Biggin in combination with either Mayo, Mathiowetz, or Rose, and Applicants respectfully submit that the rejection of record be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 843-4000.

No fee is believed owed in connection with filing of this amendment and response. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 06618-606001) for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: January 19th, 2006

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